6. NONCANCER DOSE-RESPONSE EVALUATION: RfC DERIVATION

6.1. INTRODUCTION—BACKGROUND OF THE INHALATION RfC AND ORAL RfD

Construction of a risk assessment for a toxicant requires several steps, including synthesis of information into a coherent reasonable evaluation of the hazard it presents to humans and definition of the relationship between dose of the substance and the resultant biological response. The EPA's vehicle for construction of these vital portions of a risk assessment, hazard identification and dose-response, is the inhalation reference dose (RfD) for an orally ingested toxicant or the inhalation reference concentration (RfC) for an inhaled airborne toxicant.

This chapter explains the concept and structure of the RfC as the Agency's estimate of a "safe" level, and utilizes the information documented in Chapter 5 to synthesize this estimate for diesel.

6.1.1. The Acceptable Daily Intake

Since its inception, EPA has advocated critical evaluation of data related to noncancer toxicity of compounds. When possible, quantitative estimates were calculated from combining effect levels, such as a no-observed-adverse-effect-level (NOAEL) or a lowest-observed-adverse-effect-level (LOAEL), with certain "safety factors" into an Acceptable Daily Intake (ADI). Such procedures have a wide and historical basis; the National Research Council (NRC) recommended the ADI approach in 1977 to characterize levels of pollutants in drinking water with respect to human health (NRC, 1977, 1980). These approaches, as well as the oral reference dose (RfD) and inhalation reference concentration (RfC) discussed below, are based on the assumption that a threshold exists for the human population below which no effect will occur. Basically, all of these approaches attempt to identify an estimate of a likely subthreshold concentration.

6.1.2. Oral RfD and Inhalation RfC—Dose-Response Assessments Inclusive of Uncertainty Factors

The National Academy of Sciences (NAS) report entitled "Risk Assessment in the Federal Government: Managing the Process" was issued in 1983 (NRC, 1983). Among the many fundamental concepts and principles put forth in this report was the recommendation that scientific aspects be explicitly separated from policy issues in the risk assessment process.

EPA's response included development of the RfD and guidelines on its derivation (Barnes and Dourson, 1988) and subsequent development of the parallel inhalation RfC and its formal methodology (U.S. EPA, 1994). The definition of the inhalation RfC is:

> An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime.

Similar to ADIs in intent, RfC/Ds are dose-response assessments for noncancer effects based upon a more rigorous methodology adhering to the principles set forth in the 1983 NRC report. The RfC methodology includes guidance on the consistent application to effect levels of "uncertainty factors" (UFs) rather than the ADI "safety factors " for extrapolations.

The basic quantitative formula for derivation of an RfC, given in Equation 6-1, has as its basic components an effect level and UFs. The units of an RfC are mg/m^3.

$$RfC = \frac{NOAEL}{UF} \qquad (6\text{-}1)$$

The concept of an effect level, such as the NOAEL or LOAEL, is consistent with the ADI construct. Alternatively, the benchmark dose/concentration (BMC) approach may be used as the effect level in Equation 6-1. The BMC approach applies a line-fitting model to the key data and then uses the dose-response relationship to interpolate an exposure concentration that is predicted to result in a predefined level of response (BMR), such as a 10% incidence of a lesion. The lower confidence limit on the concentration predicted to result in the BMR is designated the BMC and would be the numerator in Equation 6-1.

6.1.3. UFs—Designation and Application

The UFs, their components, and their intended usage in the RfC methodology are given in Table 6-1. As can be seen, they are fitted to the RfC definition providing consideration for *lifetime* exposure (subchronic-to-chronic duration factor) for *sensitive subgroups* (human-to-sensitive human factor) within the *human population* (animal-to-human extrapolation factor). Consideration for effect levels (a LOAEL to a NOAEL extrapolation factor) and a database factor are also part of the RfC methodology. The default values for the A and H UF are also shown with their pharmacokinetic (PK) and pharmacodynamic (PD) components, each at $10^{0.5}$, which is rounded to 3 when applied singly. The pharmacokinetic adjustments to dose provided for in derivation of RfCs (EPA, 1994) allow for application of only the PD component of this UF.

As with the safety factors for the ADI, UFs for the RfD/C are applied in a multiplicative manner. Unlike safety factors, which are almost always applied to effect levels as even factors of 10, UFs may be applied to effect levels as partial values of 10, e.g., $10^{0.5}$ (rounded to 3) or 1,

based on the circumstances. An example of application of a partial UF is for animal-to-human extrapolation with dosimetry adjustments as explained below in Section 6.1.4.

6.1.4. Animal-to-Human Extrapolation Factor in the RfC—A Human Equivalent Concentration

A major difference exists between the oral RfD and inhalation RfC in the animal-to-human (A) extrapolation procedure. Table 6-1 indicates that the A UF may have the default value of 10 and, furthermore, that this factor may be differentiated into pharmacokinetic (PK; dose to tissue) and pharmacodynamic (PD; tissue response) components. Adjustments to the externally applied factors may be made to address the PK component of this UF. The RfC methodology (U.S. EPA, 1994) provides models and procedures for adjustments with both particles and gases. In this assessment, several pharmacokinetic models, some capable of adjusting for all aspects of the PK component such as absorption, uptake, and clearance, are reviewed and evaluated. The goal of these adjustments is to derive an external concentration that would produce the same internal tissue dose in humans as in animals, i.e., to produce a Human Equivalent Concentration (HEC) from the animal effect level. When this adjustment is made, the quantitative pharmacokinetics are considered the same and the PK component of this UF is addressed. This adjustment for dosimetry is accommodated by application of a partial UF for interspecies extrapolation of $10^{0.5}$ for the remaining uncertainty about the PD component. When applied singly this factor, by policy, is rounded to 3.

Table 6-1. UFs and their default values used in EPA's noncancer RfD and RfC methodology

UF—Area of extrapolation	Default values
A—animal-to-human	10 ($10^{0.5}$ PK × $10^{0.5}$ PD)
H—human-to-sensitive human	10 ($10^{0.5}$ PK × $10^{0.5}$ PD)
S—subchronic-to-chronic	10
L—LOAEL-to-NOAEL	10
D—incomplete-to-complete data	10

6.1.5. Basic Procedures for Derivation of an RfC—Identification of the Critical Effect, the Principal Study, Application of UF, and Assignment of Confidence Level

The goal of the RfC/D methodologies is to provide rationale and guidance on a quantitative approach in evaluating toxicity data to derive a dose-response assessment. Equation 6-1 is a condensation of the RfC process and serves as a basis for discussing the procedures for its derivation. Having a NOAEL for this equation implies that a specific adverse effect has been identified and that there is documentation that this effect does not occur at this particular concentration, i.e., the NOAEL.

RfC derivation provides for evaluation of the toxicity database to identify a "critical effect," which is defined as "the first adverse effect, or its known precursor, that occurs as the dose rate increases." Analysis of the database also allows for choice of a "principal study," "the study that contributes most significantly to the qualitative and quantitative risk," in characterizing the dose-response of the critical effect. To fulfill the definition of the RfC, the critical effect would have to be consonant with the definition of the RfC given above, e.g., relevant to humans and observed under chronic, long-term conditions. Other studies that are pertinent to identifying the dose-response or threshold for the effect are included in the derivation as supporting studies. Thus, the NOAEL in Equation 6-1 would be based on the absence of the critical effect as documented in the principal study.

Assignment of an appropriate UF would be accomplished in consideration of the information available on the specific chemical as per Table 6-1. General guidelines were discussed briefly in this introductory section and are discussed at length in the RfC Methods (U.S. EPA, 1994). As explained above, assignment of specific values of UF may have both policy and science implications. General policy is to provide clear explanatory text with each UF assignment. Composite UF values vary widely. In cases where information on the NOAEL is well defined in a known sensitive subgroup of humans, the UF may be 1. With sparse information, UF values have ranged up to 3000. If none of the areas of extrapolation in Table 6-1 are addressed (i.e., all areas of uncertainty are applicable), then no RfC is derived.

Confidence statements are synthesized for each RfC. They are meant to serve as a repository for statements that clearly communicate associated uncertainties, establish and dichotomize policy from scientific bases, make clear specific limitations and strengths, and express any other concerns reflecting on the overall quality of the assessment (U.S. EPA, 1994; Ohanian et al., 1997). The RfC/D methodologies allow for high, medium, and low levels of confidence, with the level being assigned subsequent to an analysis as above. Levels are surmised for both the overall database and the principal study/ies, with the database confidence taking precedence over that assigned to the study. In general, the level of confidence is inversely related to both the composite UF and the likelihood that the RfC would change with the availability of new

information; an RfC based on a sensitive effect in a sensitive human subgroup as reported in a exemplary study with a composite UF of < 30 would more than likely be one of high confidence.

6.2. ISSUES IN DERIVATION OF THE DIESEL RfC

Information available on diesel particulate matter (DPM) is that in other databases and therefore includes several areas of controversy and uncertainty. This section introduces issues concerning DPM. Subsequent sections will then more fully examine and consider these issues.

6.2.1. Chronic Noncancer Effects in Humans—Relevancy of Rodent Data

Current information shows that humans and rodents share some noncancer responses to poorly soluble particles such as DPM that are qualitatively similar. These analogous responses suggest that a potential commonality exists between humans and rodents in the underlying mode(s) of action of DPM. These analogous responses and shared steps in the mode of action do not appear to extend to the tumorigenic response seen in one particular rodent species, the rat. As discussed in other sections of this document, the relevance to humans of the tumorigenic response in rat lungs occurring under particle overload conditions is problematic.

6.2.2. Pulmonary Pathology and Immunologic Effects as Critical Effects

Recent investigations in both laboratory animals and humans in clinical settings have associated exposure to DPM with immunologic effects, especially enhanced allergenicity. The relationship between pulmonary histopathology and allergenic effects is compared and contrasted in the choice of pulmonary histopathology as a scientifically defensible critical effect upon which to base this assessment.

6.2.3. Application of UFs

As discussed above, applications of UF consider both science and policy. Because of the extensive database of well-conducted long-term chronic studies in several species, much is known about the effects of DPM on the lung as target organ. Relatively few areas of uncertainty are applicable to the diesel database. Moreover, the application of a pharmacokinetic model in this assessment obviates a portion of the animal-to-human UF as explained above. Questions concerning the application of uncertainty for consideration of the enhanced allergenic effects are presented and discussed.

6.2.4. Relationship of DPM to Ambient Levels of $PM_{2.5}$

DPM is acknowledged as a component of the fine particulate matter ($PM_{2.5}$) present in ambient air, especially in urban areas. It is known that compared with $PM_{2.5}$, DPM has a higher

proportion of fine and ultrafine particles and a higher content of organic compounds absorbed onto the carbon core. DPM could thus be considered a subcategory of $PM_{2.5}$ with greater toxicologic potential from the higher organic compound content, which would penetrate more efficiently into the alveolar compartment because of the preponderance of small particles in DPM.

6.3. APPROACH FOR DERIVATION OF THE RfC FOR DIESEL ENGINE EMISSIONS

6.3.1. Consideration of Long-Term Inhalation Studies

Twelve long-term (>1 year) laboratory animal inhalation studies of diesel engine emissions have been conducted. These studies focused on effects in the pulmonary region. Studies at the Inhalation Toxicology Research Institute (ITRI) and the Japanese Health Effects Research Program (HERP) consisted of large-scale chronic exposures, with exposed animals being designated for the study of various endpoints and at various time points (Ishinishi et al., 1986, 1988; Mauderly et al., 1987a,b, 1988; Henderson et al., 1988; Wolff et al., 1987). Each research program is represented by multiple published accounts of results. These programs were selected as the principal basis for deriving the RfC because each contains studies that identify an LOAEL and an NOAEL for respiratory effects after chronic exposure (see Section 6.2) as well as pulmonary histopathology. Effects in the upper respiratory tract and other organs were not found consistently in chronic animal exposures.

6.3.2. Derivation of a HEC—Application of a Pharmacokinetic Model

PK models may be used to project across species concentrations of a toxicant that would result in equivalent internal doses. When used for these purposes, PK models may be termed dosimetric models. Chapter 3 reviewed and evaluated a number of dosimetric models applicable to DPM. The model developed by Yu and Yoon (1990) that accounts for species differences in deposition efficiency, normal and particle overload lung clearance rates, respiratory exchange rates and particle transport to lung-associated lymph nodes was selected for use in this assessment. A major assumption in this model is that the particle overload phenomenon occurs in humans and in rats at equivalent lung burdens expressed as mass per unit surface area (Yu and Yoon, 1990). This assumption allows for the development of a diesel particle-specific human retention model and therefore allows extrapolation from rat studies to human exposures. See Chapter 3 for further discussion of the model and Appendix B for complete specifics on the use of the model.

A principal and critical decision in utilizing any dosimetric model is the measure of dose. DPM is composed of an insoluble carbon core with a surface coating of relatively soluble organic

constituents. Because macrophage accumulation, epithelial histopathology, and reduced clearance have been observed in rodents exposed to high concentrations of chemically inert particles (Morrow, 1992), the toxicity of DPM may result from the carbon core rather than from the associated organics. However, the organic component of diesel particles, consisting of a large number of polycyclic aromatic hydrocarbons and heterocyclic compounds and their derivatives (Chapter 2), may also play a role. It is not possible to separate the carbon core from the adsorbed organics to compare the toxicity. Therefore, the whole particle was used as the measure of dose. See Chapters 6 and 9 for further details.

The input data required to run the dosimetric model include the particle size characterization expressed as mass median aerodynamic diameter (MMAD) and the geometric standard deviation (σg). In the principal and supporting studies used for the RfC derivation, these parameters are measured using different methods and reported in different levels of detail. Simulation data presented by Yu and Xu (1986) show that across a range of MMAD and σg inclusive of the values reported in these studies, the pulmonary deposition fraction differs by no more than 20%. The minimal effect of even a large distribution of particle size on deposition probably results because the particles are still mostly in the submicron range and deposition is influenced primarily by diffusion. It has also been shown, however, that the particle characteristics in a diesel exhaust exposure study depend very much on the procedures used to generate the chamber atmosphere. Because of the rapid coagulation of particles, the volume and temperature of the dilution gas are especially important. The differences reported in particle sizes and distributions in various studies likely reflected real differences in the exposure chambers as well as different analytical methods. Because the particle diameter and size distribution were not reported in the two lowest exposure concentrations in the HERP studies, it was decided to use a representative DPM particle size of MMAD = 0.2 μm and $\sigma g = 2.3$ (values typically reported for DPM) for modeling of lung burden. For consistency, the lung burdens for the other studies were also calculated using this assumption. The difference in the HEC using the default particle size compared with the actual reported particle size is no more than 4% in the HERP study and 19% in the ITRI study.

6.4. CHOICE OF THE CRITICAL EFFECT—RATIONALE AND JUSTIFICATION

6.4.1. Mode-of-Action and Candidate Effects

Mode-of-action information about respiratory effects from diesel exposure indicates that the pathogenic sequence following the inhalation of diesel exhaust begins with the phagocytosis of diesel particles by alveolar macrophages (AMs). These activated AMs release chemotactic factors that attract neutrophils and additional AMs. As the lung burden of DPM increases, there are aggregations of particle-laden AMs in alveoli adjacent to terminal bronchioles, increases in the

number of Type II cells lining particle-laden alveoli, and the presence of particles within alveolar and peribronchial interstitial tissues and associated lymph nodes. The neutrophils and AMs release mediators of inflammation and oxygen radicals, and particle-laden macrophages are functionally altered, resulting in decreased viability and impaired phagocytosis and clearance of particles. The latter series of events may result in pulmonary inflammatory, fibrotic, or emphysematous lesions like those described in the studies reviewed in Chapter 7. Epidemiologic studies of occupationally exposed people provide suggestive evidence for a respiratory effect. Although detailed information describing the pathogenesis of respiratory effects in humans is lacking, the effects reported in studies of humans exposed to diesel exhaust lend qualitative support to the findings in controlled animal studies and therefore to this basic mode of action.

Evidence from the available toxicological data on diesel exhaust consistently indicates that inhalation of diesel exhaust can be a respiratory hazard, based on findings in multiple controlled laboratory animal studies in several species with suggestive evidence from human occupational studies, most of which are described and evaluated in Chapter 7. The endpoints of concern include biochemical, histopathological, and functional changes in the pulmonary and tracheobronchial regions.

The occurrence of a lung cancer response in rats under conditions of "clearance overload" from diesel exhaust/DPM has been discussed elsewhere in this document as being possibly unique to the rat and of problematic relevance to human lung responses. Yet effects in the rat lung are being proposed as the basis for the RfC. There are several reasons why these effects are considered valid and relevant for RfC derivation. First, the effects considered, inflammation (inflammatory cell infiltration) and fibrosis, are noncancer effects. Second, similar noncancer effects are seen in other species (mouse, hamster), albeit under conditions of higher exposure than rats, and these species do not manifest a cancer response. Third, rats and humans do exhibit similar noncancer responses (macrophage response and interstitial fibrosis) to less toxic particles (i.e., coal dust) and to lower concentrations of poorly soluble particles such as DPM. Thus, when viewed across species the pulmonary effects of inflammation and fibrosis are considered dissociable from the cancer response and of likely relevance to humans.

Some evidence suggests liver and kidney changes in animals exposed to diesel exhaust. There have also been some indications of neurotoxicity at high concentrations of diesel exhaust. These data, however, are inadequate to indicate that a hazard exists for these endpoints.

Studies of other endpoints, including reproductive and developmental toxicity, in controlled animal exposures have shown no potential hazard.

Recent evidence has accumulated for effects of diesel exhaust and DPM on respiratory system-related immune function, especially enhanced or exacerbated allergenicity. Chapter 5 describes studies of human cells in vitro as well as human nasal instillation and inhalation studies

that have demonstrated the potential for DPM to enhance allergic inflammatory responses. This effect included observations wherein increases of IgE were produced in nasal lavage, especially when DPM was instilled concomitantly with allergen in atopic rhinitic subjects. DPM has also been shown to enhance histamine-induced increase of certain inflammatory mediators such as IL-8 and GM-CSF. Exposure of healthy human subjects to dilute diesel exhaust (300 µg) for 1 hour with intermittent exercise led to an acute mediator and cellular inflammatory response in the airways and peripheral blood.

6.4.2. Rationale and Justification

The choice of critical effect for DPM must be consonant with the definition given above and made in consideration of the purposes of the RfC, e.g., a lifetime continuous exposure that is without adverse effects. From the discussion above, the principal candidate critical effects are the pulmonary histopathological changes in rats and enhanced allergenic effects in the upper airways of animals and humans. The following points compare and contrast these effects:

- Pulmonary histopathology is shown consistently in several species with clear dose-response under long-term realistic exposure scenarios. Allergenic effects are shown consistently in both animal and clinical human studies but, dose-response and concentration × times (C × t) relationships are not available under any exposure scenario.

- The relevance of these candidate effects to humans is each subject to qualifications. Enhanced allergenic effects have been demonstrated in humans. However, the observations were mostly in sensitized individuals exposed via nasal instillation, a questionable route, and to relatively high bolus doses. The pulmonary histopathology observed in rat studies is only marginally supported by effects that may occur in humans.

- Events that stimulate inflammatory processes may underlie both these effects. Fibrogenesis is necessarily preceded and accompanied by inflammation. Events such as enhancement of inflammatory cytokines have been associated with allergenic enhancement.

As the RfC is a dose-response assessment for effects encountered under conditions of chronic exposure, pulmonary histopathology would therefore be the most robust and defensible

choice for the critical effect. Long-term, dose-response, and mode-of-action information could warrant reconsideration of allergenic effects as being critical or possibly co-critical.

6.5. PRINCIPAL STUDIES FOR INHALATION RfC DERIVATION

The experimental protocol and results for the principal studies demonstrating and characterizing the critical effect are discussed in Chapter 7 and Appendix A and are briefly reviewed here. In studies conducted at ITRI, rats and mice were exposed to target DPM concentrations of 0, 0.35, 3.5, or 7 mg/m^3 for 7 h/day, 5 days/week for up to 30 mo (rats) or 24 mo (mice) (Mauderly et al., 1988). A total of 364 to 367 rats per exposure level were exposed and used for studies examining different endpoints such as carcinogenicity, respiratory tract histopathology and morphometric analysis, particle clearance, lung burden of DPM, pulmonary function testing, lung biochemistry, lung lavage biochemistry and cytology, immune function, and lung cell labeling index. Subsets of animals were examined at 6, 12, 18, and 24 mo of exposure and surviving rats were examined at 30 mo. Diesel emissions from a 5.7-L engine operated on a Federal Test Procedure urban driving cycle were diluted and fed into the exposure chambers. Particle concentrations were measured daily using a filter sample, and weekly grab samples were taken to measure gaseous components including carbon monoxide, carbon dioxide, nitrogen oxides, ammonia, and hydrocarbons. The actual DPM concentrations for the low-, medium-, and high-exposure levels were 0.353, 3.47, and 7.08 mg/m^3, respectively. Mass median diameters (geometric standard deviations) determined using an impactor/parallel flow diffusion battery were 0.262 (4.2), 0.249 (4.5), and 0.234 (4.4) for the low-, medium-, and high-exposure groups, respectively.

Lung wet weight to dry weight ratio was increased significantly in the two highest exposure groups. Qualitative descriptions of the histopathological results in the respiratory tract are found in Mauderly et al. (1987a, 1988), Henderson et al. (1988), and McClellan et al. (1986). Aggregates of particle-laden AMs were seen after 6 mo in rats exposed to 7 mg/m^3 DPM target concentrations, and after 1 year of exposure histopathological changes were seen, including focal areas of epithelial metaplasia. Fibrosis and metaplasia increased with duration of exposure and were observable in the 3.5 and 7 mg/m^3 groups of rats at 24 mo. Changes in the epithelium included extension of bronchiolar cell types into the alveoli. Focal thickening of the alveolar septa was also observed. Histopathological effects were seen in areas near aggregations of particle-laden AMs. The severity of inflammatory responses and fibrosis was directly related to the exposure level. In the 0.35 mg/m^3 group of rats, there was no inflammation or fibrosis. Although the mouse lungs contained higher lung burdens of DPM per gram of lung weight at each equivalent exposure concentration, there was substantially less inflammatory reaction and fibrosis

than was the case in rats. Fibrosis was observed only in the lungs of mice exposed at 7 mg/m^3 DPM and consisted of fine fibrillar thickening of occasional alveolar septa.

Groups of 16 rats and mice (8/sex) were subjected to bronchoalveolar lavage after 6, 12, 18, and 24 (rats only) mo of exposure (Henderson et al., 1988). Lung wet weights were increased at 7 mg/m^3 in mice and rats at all time points and in mice at 3.5 mg/m^3 at all time points after 6 mo. An increase in lavagable neutrophils, indicating an inflammatory response in the lung, was seen at 3.5 and 7 mg/m^3 in rats and mice at most time points. An increase in protein content of the bronchoalveolar lavage fluid was observed in rats exposed to 3.5 or 7 mg/m^3 at 12 and 18 mo but not at 24 mo. Increased protein content was also seen in mice at the two higher concentrations at all time points. Increases in lavage fluid content of lactate dehydrogenase, glutathione reductase, β-glucuronidase, glutathione, and hydroxyproline were observed in rats and mice exposed to 3.5 or 7 mg/m^3 at various time points. At the lowest exposure level, no biochemical or cytological changes occurred in the lavage fluid or in lung tissue in either Fischer 344 rats or CD-1 mice.

Mauderly et al. (1988; see also McClellan et al., 1986) examined the impairment of respiratory function in rats exposed according to the protocol described above. After 24 mo of exposure to 7 mg/m^3 DPM, mean TLC, C_{dyn}, quasi-static chord compliance, and CO diffusing capacity were significantly lower than control values, and nitrogen washout and percentage of forced vital capacity expired in 0.1 s were significantly greater than control values. There was no evidence of airflow obstruction. Similar functional alterations were observed in the rats exposed to 3.5 mg/m^3 DPM, but such changes usually occurred later in the exposure period and were generally less pronounced. There were no significant decrements in pulmonary function for the 0.35 mg/m^3 group at any time during the study.

Wolff et al. (1987) investigated alterations in particle clearance from the lungs of rats in the ITRI study. Progressive increases in lung burdens were observed over time in the 3.5 and 7.0 mg/m^3 exposure groups. There were significant increases in 16-day clearance half-times of inhaled radiolabeled particles of gallium oxide (0.1 μm MMAD) as early as 6 mo at the 7.0 mg/m^3 level and 18 mo at the 3.5 mg/m^3 level; no significant changes were seen at the 0.35 mg/m^3 level. Rats that inhaled fused aluminosilicate particles (2 μm MMAD) radiolabeled with cesium after 24 mo of diesel exhaust exposure showed increased clearance half-times in the 3.5 and 7.0 mg/m^3 groups.

In the HERP studies, histopathological effects of diesel exhaust on the lungs of rats were investigated (Ishinishi et al., 1986, 1988). In this study, both light-duty (LD, 1.8-L) and heavy-duty (HD, 11-L) diesel engines were operated under constant velocity and load conditions. The exhaust was diluted to achieve target concentrations of 0.1 (LD only), 0.4 (LD and HD), 1 (LD and HD), 2 (LD and HD), and 4 (HD only) mg/m^3 DPM. Particle concentrations were

determined by filter samples. Actual concentrations were 0.11, 0.41, 1.18, and 2.32 mg/m^3 for the light-duty engine and 0.46, 0.96, 1.84, and 3.72 mg/m^3 for the heavy-duty engine. Fischer 344 rats (120 males and 95 females per exposure level for each engine type) were exposed for 16 h/day, 6 days/week for 30 mo. Particle size distributions were determined using an Andersen cascade impactor and an electrical aerosol analyzer. At the 24-mo sampling, the MMAD and distribution (σg) were 0.22 (2.93) and 0.19 (2.71) for the light-duty engine groups at 2.32 and 1.18 mg/m^3, respectively, and 0.27 (3.18) and 0.22 (2.93) for the heavy-duty engine groups at 3.72 and 1.84 mg/m^3, respectively (Ishinishi et al., 1988). The number and timing of the samples are not clear from the published reports, nor is it clear which method was used for the results reported above. Particle size data were not reported for the other exposure groups, although measurements for all groups, including those of ITRI, are quite similar to one another. Hematology, clinical chemistry, urinalysis, and light and electron microscopic examinations were performed. The body weight of females exposed to 4 mg/m^3 DPM was 15% to 20% less than that of controls throughout the study. No histopathological changes were observed in the lungs of rats exposed to 0.4 mg/m^3 DPM or less. At concentrations above 0.4 mg/m^3 DPM, accumulation of particle-laden AMs was observed. In areas of AM accumulation, there was bronchiolization of the alveolar ducts, with bronchiolar epithelium replacing alveolar epithelium. Proliferation of brochiolar epithelium and Type II cells was observed. In these areas, edematous thickening and fibrosis of the alveolar septum were seen. Fibrosis of the alveolar septum developed into small fibrotic lesions. These are collectively referred to as hyperplastic lesions by the authors and their incidence is reported.

From a total of 123 to 125 animals examined (approximately equal numbers of males and females), hyperplastic lesions were reported in 4, 4, 6, 12, and 87 animals in the light-duty engine groups exposed to 0, 0.11, 0.41, 1.18, and 2.32 mg/m^3 DPM, respectively, and in 1, 3, 7, 14, and 25 animals in the heavy-duty engine groups exposed to 0, 0.46, 0.96, 1.84, and 3.72 mg/m^3 DPM, respectively. Statistical analysis of these results was not reported, but there was no difference in the severity ascribed to changes in pulmonary pathology at similar exposure concentrations between the LD and the HD series.

The ITRI and HERP studies are complementary for identifying the critical effect and its LOAEL and NOAEL. The ITRI study provides results on many different endpoints reflecting pulmonary toxicity, and the effect levels are the same, but the LOAEL and NOAEL are different by a factor of 10. In the HERP study, the concentrations differ by a factor of 2-4, but only histopathology is reported. Taken together, these two studies (including several published reports for the ITRI study) provide good definition of the low-concentration effects of diesel emissions.

The HERP study identifies LOAELs for rats exposed chronically at 1.18 and 0.96 mg/m^3 (actual exposure) for the LD and HD series, respectively, and NOAELs at 0.41 and 0.46 mg/m^3

(actual) for the LD and HD series. The ITRI studies identify a NOAEL for biochemical, histopathological, and functional changes in the pulmonary region at 0.35 mg/m^3 (LOAEL = 3.5 mg/m^3). The HECs for the principal studies were obtained using the deposition and retention model of Yu and Yoon (1990), as discussed previously. The HEC calculation is based on the assumption that the estimate for the human exposure scenario (a 70-year continuous exposure) should result in an equivalent dose metric, expressed as mass of diesel particle carbon core per unit of pulmonary region surface area, to that associated with no effect at the end of the 2-year rat study. To obtain the HEC, the lung burden in the rat study is calculated using the exposure regimen (concentration, number of hours per day, and days per week) and values for rat tidal volume, functional residual capacity, and breathing frequency. A continuous human exposure resulting in the same final lung burden is calculated and is the HEC. The HEC values corresponding to the animals' exposure levels in the principal studies are shown in Table 6-2, along with a designation of the concentrations as AEL (adverse-effects level) or NOAEL; the LOAELs (HEC) are 0.30, 0.36, and 0.36 mg/m^3. These values, along with the LOAELs from other studies (discussed below), show strong support for an experimental threshold in rats in the range of 0.15 to 0.3 mg/m^3 DPM. The highest NOAEL (HEC), which is below all LOAELs (HEC), is 0.155 mg/m^3 DPM from the HERP heavy-duty diesel study. This NOAEL (HEC) is selected as the basis for the RfC calculation.

6.6. SUPPORTING STUDIES FOR INHALATION RfC DERIVATION

Chronic inhalation studies using male F344 rats and male Hartley guinea pigs were carried out at the General Motors (GM) Research Laboratories (Barnhart et al., 1981, 1982). Exposures to target concentrations of 0.25, 0.75, and 1.5 mg/m^3 DPM were generated 20 h/day, 5.5 days/week for up to 2 years. Exposures at 0.75 and 1.5 mg/m^3 for 2 weeks to 6 mo were reported by Barnhart et al. (1981, 1982). The focus of these studies is on electron micrographic morphometry, and very little descriptive light microscopic histology is reported. These data show that no appreciable changes in morphometric parameters occurred after a 2-year exposure

Table 6-2. Human equivalent continuous concentrations from the principal studies

Study	Exposure concentration (mg/m^3)	AEL/NOAEL[a]	HEC[b] (mg/m^3)
HERP-light duty	0.11	NOAEL	0.038
	0.41	NOAEL	0.139
	1.18	AEL	0.359
	2.32	AEL	0.571
HERP-heavy duty	0.46	NOAEL	0.155
	0.96	AEL	0.303
	1.84	AEL	0.493
	3.72	AEL	0.911
ITRI	0.353	NOAEL	0.042
	3.47	AEL	0.360
	7.08	AEL	0.582

[a]AEL: adverse-effects level; NOAEL: no-observed-adverse-effect level.
[b]HEC: human equivalent concentration obtained from applying the dosimetric model of Yu and Yoon (1990).

to 0.25 mg/m^3, while exposure to 0.75 or 1.5 mg/m^3 DPM resulted in increased thickness of alveolar septa and increased number of various types of alveolar cells. Increased numbers of PMNs and monocytes were lavaged from rats exposed to 0.75 or 1.5 mg/m^3, and biochemical changes occurred in lung tissue at these concentrations (Misiorowski et al., 1980; Eskelson et al., 1981; Strom, 1984). These studies demonstrate a LOAEL of 0.796 mg/m^3 DPM and a NOAEL of 0.258 mg/m^3 DPM for male guinea pigs in a chronic study for respiratory endpoints, including light and electron microscopy, lavage cytology, and lung tissue biochemistry.

A 15-mo inhalation study was performed by Southwest Research Institute for General Motors (Kaplan et al., 1983). Male F344 rats, Syrian golden hamsters, and A/J mice were exposed to diluted diesel exhaust at target concentrations of 0.25, 0.75, and 1.5 mg/m^3 for 20 h/day and 7 days/week. Focal accumulation of particle-laden AMs was associated with minimal to mild fibrosis of the alveolar wall. Based on accumulation of particle-laden macrophages, this study identifies a LOAEL at 0.735 mg/m^3 and a NOAEL at 0.242 mg/m^3.

In a study performed by NIOSH (Lewis et al., 1986, 1989; Green et al., 1983), male and female F344 rats and male Cynomolgus monkeys were exposed to target levels of 2 mg/m^3 diesel particles. Accumulations of black-pigmented alveolar macrophages were seen in the alveolar ducts of rats adjacent to terminal bronchioles, and epithelial lining cells adjacent to collections of pigmented macrophages showed marked Type II cell hyperplasia. No evidence of impaired pulmonary function as a result of the exposure to diesel exhaust was found in rats. Histological examination of lung tissue from monkeys exposed for 24 mo in the same regimen used for rats revealed aggregates of black particles, principally in the distal airways of the lung. No fibrosis, focal emphysema, or inflammation was observed. The monkeys exposed to diesel exhaust demonstrated small-airway obstructive disease. This study demonstrates a LOAEL for rats and monkeys at a diesel particle concentration of 2 mg/m^3. Although the data suggest that the pulmonary function effect in primates more closely resembles that in humans, this study had only one exposed group, making evaluation of dose response impossible. Thus, it was not considered sufficient to eliminate consideration of the strong rodent database.

Heinrich et al. (1986; see also Stöber, 1986) exposed male and female Syrian golden hamsters, female NMRI mice, and female Wistar rats to diesel engine emissions with a 4.2 mg/m^3 particulate concentration. Lung weights were increased by a factor of 2 or 3 in rats and mice after 2 years of exposure, and in hamsters the lung weights were increased by 50% to 70%. Although histopathological examination revealed different levels of response among the three species, histopathological effects were seen in all species and effects on pulmonary function were observed in rats and hamsters. This study demonstrates a LOAEL of 4.2 mg/m^3 in rats for respiratory system effects.

The effects of diesel exhaust on the lungs of 18-week-old male Wistar rats exposed to 8.3 ± 2.0 mg/m^3 particulate matter were investigated by Karagianes et al. (1981). Histological examinations of lung tissue noted focal aggregation of particle-laden alveolar macrophages, alveolar histiocytosis, interstitial fibrosis, and alveolar emphysema. Lesion severity was related to length of exposure. No exposure-related effects were seen in the nose, larynx, or trachea. This study demonstrates a LOAEL of 8.3 mg/m^3 DPM for respiratory effects after chronic exposure of rats to diesel emissions.

Lung function was studied in adult cats chronically exposed to diesel exhaust concentrations of 6.34 mg/m^3 for the first 61 weeks and 6.7 mg/m^3 from weeks 62 to 124. No definitive pattern of pulmonary function changes was observed following 61 weeks of exposure; however, a classic pattern of restrictive lung disease was found at 124 weeks (Pepelko et al., 1980).

Heinrich et al. (1995) exposed Wistar rats to diesel exhaust at DPM concentrations of 0.8, 2.5, and 7 mg/m^3, 18 h/day, 5 days/week for 24 mo. Body weights were significantly decreased in

the two higher exposure groups. Bronchoalveolar hyperplasia and interstitial fibrosis of increasing incidence and severity at greater concentrations were seen in all exposure groups. This study demonstrates a LOAEL of 0.8 mg/m^3.

Nikula et al. (1995) exposed Fischer 344 rats to diesel exhaust at DPM concentrations of 2.4 and 6.3 mg/m^3 16 h/day, 5 days/week for 23 mo. Survival was decreased in the high-exposure males, while body weights were reduced in both males and females in the high-exposure group. Pulmonary hyperplasia, inflammation, and fibrosis were seen in a high percentage of rats in both exposure groups. The high exposure concentrations precluded use of this study for development of an RfC.

Werchowski et al. (1980a) reported a developmental study in rabbits exposed on days 6 through 18 of gestation to a 1-in-10 dilution of diesel exhaust (DPM concentration $\approx$ 12 mg/m^3). Exposure to diesel emissions had no effect on maternal toxicity or the developing fetuses. In a companion study (Werchowski et al., 1980b), 20 SD rats were exposed for 8 h/day during days 5 to 16 to a target concentration of 12 mg/m^3 of DPM. Fetuses were examined for external, internal, and skeletal malformations, and the numbers of live and dead fetuses, resorptions, implants, corpora lutea, fetal weight, litter weight, sex ratio, and maternal toxicity were recorded. No conclusive evidence of developmental effects was observed in this study.

In an EPA-sponsored reproductive study summarized by Pepelko and Peraino (1983), CD-1 mice were exposed to a target concentration of 12 mg/m^3 DPM for 8 h/day and 7 days/week. The F_0 and F_1 animals were exposed for 100 days prior to breeding, and 100 mating pairs were randomly assigned to four exposure groups of 25 each. Viability counts and pup weights were recorded at 4, 7, and 14 days after birth and at weaning. No treatment-related effects on body weight in F_0 mice or in F_1 animals through weaning or in mating animals through gestation were found. No treatment-related effects on gestation length, percent fertile, litter size, or pup survival were observed. The only organ weight difference was an increase in lung weight in exposed F_0 and F_1 mice (lung weight and lung weight/body weight) and in F_2 males (lung weight/body weight). Based on this study, a NOAEL for reproductive effects in rats is identified at 12 mg/m^3 DPM.

The reproductive and developmental studies described in Chapter 5 show that effects in the respiratory system are the most sensitive effects that result from diesel exhaust exposures. These studies add to the confidence that a variety of noncancer effects have been studied and are required for a designation of high confidence in the database and the RfC (discussed further below).

Several epidemiologic studies have evaluated the effects of chronic exposure to diesel exhaust on occupationally exposed workers. The human studies, taken together, are suggestive but inconclusive of an effect on pulmonary function, as described in Chapter 7. The studies are

not directly useful for deriving the RfC because of inadequate ability to directly relate the observed effects to known concentrations of DPM. The studies are confounded by coexposures to other particles or by a lack of measurement of particle exposure.

6.6.1. Respiratory Tract Effects in Species Other Than the Rat

In several of the chronic inhalation studies described in Chapter 7, one or more species other than the rat were also exposed and examined for toxic effects. These provide a basis for comparison of the effects in rats with the effects in other species. In the study performed at ITRI (Henderson et al., 1988; Mauderly et al., 1988), male and female CD-1 mice were exposed similarly to the rats. The LOAEL and NOAEL in rats and mice from this study would be the same, with the NOAEL for respiratory tract effects being 0.35 mg/m^3 DPM (duration adjusted NOAEL is 0.074 mg/m^3), although some differences in the severity of the effect were apparent.

In the study conducted by the GM Biomedical Science Department (Barnhart et al., 1981, 1982; Strom, 1984; Gross, 1981), male Hartley guinea pigs as well as F344 rats were chronically exposed to 0.258, 0.796, and 1.53 mg/m^3 DPM. The evidence from this study leads to the conclusion that the LOAEL and NOAEL for rats and guinea pigs are the same, although important differences in the endpoints were reported in the two species. The NOAEL is 0.258 mg/m^3 (duration-adjusted NOAEL is 0.17 mg/m^3).

Kaplan et al. (1982) reported a subchronic study in F344 rats, A/J mice, and Syrian golden hamsters exposed to 1.5 mg/m^3 DPM. The histopathological observations, including AM accumulation and associated thickening of the alveolar wall, were described together, with no distinction between species, suggesting that the observed effects were similar in the species examined. Kaplan et al. (1983) reported a 15-mo study in which F344 rats, A/J mice, and Syrian golden hamsters were exposed to 0.25, 0.75, or 1.5 mg/m^3 DPM. No exposure-related lesions were found in tissues other than the respiratory tract. Based on particle-laden AM accumulation, this study identifies a LOAEL at 0.735 mg/m^3 and a NOAEL at 0.242 mg/m^3. The descriptions provided suggest that the pulmonary effects were similar across the three species examined, but this conclusion is compromised by the lack of detailed reporting and the possibility of infection in rats and poor animal health (as evidenced by poor growth) in hamsters. The duration-adjusted NOAEL is 0.202 mg/m^3.

Lewis et al. (1986, 1989) exposed rats and monkeys to 2 mg/m^3 DPM for 2 years and reported pulmonary function and histopathology. Pulmonary function was affected in both species, although with a different pattern of response, as discussed in Chapter 5. Significant differences were observed in the histopathological response. In monkeys, slight particle accumulation was observed, but no fibrosis, focal emphysema, or inflammation was present. Rat

lungs in this experiment showed AM accumulation, multifocal histiocytosis, and associated fibrosis and inflammatory cells in the interstitium.

Heinrich et al. (1986) exposed Wistar rats, Syrian golden hamsters, and NMRI mice chronically to 4 mg/m^3 DPM. Lung weight was increased 1.5-fold in hamsters, twofold in mice, and threefold in rats. The activity of enzymes recovered in bronchoalveolar lavage was increased to roughly the same extent in rats, mice, and hamsters. Hamsters showed thickened alveolar septa and slight epithelial hyperplasia, with no AM accumulation. Mice also showed epithelial hyperplasia and interstitial fibrosis. Rat lungs had severe inflammatory changes, thickened alveolar septa, hyperplasia, and metaplasia. This study presents the clearest indication of a possibly greater severity of noncancer effects in rats compared with other rodent species. It also suggests that the effect in rats may be qualitatively different, with AM accumulation playing a greater role in pathogenesis in rats than in other rodent species.

Heinrich et al. (1995) also compared effects of chronic diesel exposure on rats and two strains of mice exposed to fairly high concentrations of diesel particles. Similar lung burdens were reported in rats and mice on the basis of particle mass per unit lung wet weight. Lung weight was increased to about the same extent in rats and mice. However, the study is focused on cancer effects, and insufficient information is provided to make a detailed comparison of noncancer histopathology in rats and mice.

Several of the studies described above and in Chapter 7 suggest a significant difference in the carcinogenic response of rats and other experimental animal species. It is less clear whether such a difference holds for noncancer effects at lower exposure levels. The studies described above show similar effect levels for different species for effects that occur earlier or at lower exposure concentration, including accumulation of particles, bronchoalveolar lavage measurements, lung weight, and minor epithelial thickening and hyperplasia. At higher diesel concentrations there are clear differences between rats and the other species tested, especially in the progression to more severe histopathologically observed endpoints, such as hyperplasia, metaplasia, and inflammatory response. Thus the NOAEL for chronic effects of diesel does not appear to be substantially different among species, although there is some suggestion in the literature of a more sensitive as well as a qualitatively different response in rats. This comparison is weakened because the published reports often give less emphasis to noncancer responses and because the effects in rats and other species are not always measured or reported in the same way. The pathogenesis of diesel exhaust effects has not been studied as thoroughly in any other species as it has in the rat. For example, no specific measurement of particle clearance from the lung has been reported in any species other than the rat. Within the resolving power of the available studies, it is concluded that there is limited evidence for a difference in the NOAEL for noncancer effects across species, but the evidence is not adequate to quantitatively define the difference,

especially at low exposure concentrations. Hence there is no clearly more appropriate species on which the RfC derivation for noncancer effects should be based.

Mice were included in the ITRI, Kaplan et al. (1982), and Heinrich et al. (1986, 1995) studies. The Heinrich studies used a single exposure to high concentrations and are supportive of the other results in mice but are not appropriate to define a LOAEL for mice. The Kaplan study defines an LOAEL and NOAEL of 0.735 and 0.242 mg/m^3 DPM, respectively. The duration-adjusted LOAEL and NOAEL are 0.613 and 0.202 mg/m^3, respectively. The ITRI study defined the adjusted LOAEL and NOAEL at 0.723 and 0.074 mg/m^3, respectively. Because the dose spacing is so wide in the ITRI study, the Kaplan study is more appropriate for defining a NOAEL. Likewise, the Kaplan et al. study is the only multiple-dose study in hamsters, and it defines the same LOAEL and NOAEL for hamsters as for mice. The GM study is the only chronic study in guinea pigs, and it defines the LOAEL and NOAEL for this species at 0.796 and 0.258 mg/m^3, respectively. The adjusted LOAEL and NOAEL for guinea pigs from the GM study are 0.52 and 0.17 mg/m^3, respectively. The effects levels for mice, hamsters, and guinea pigs are similar to the duration-adjusted LOAEL and NOAEL for rats, which are 0.723 mg/m^3 (ITRI study) and 0.26 mg/m^3 (from Ishinishi et al., 1988), respectively. If the RfC were to be derived based on the duration-adjusted NOAEL, the rat data would be preferred because of the more complete database of chronic rat studies and the more complete presentation of the noncancer endpoints in the rat studies.

The method for deriving inhalation RfCs (U.S. EPA, 1994) includes dosimetric adjustments of animal exposure to arrive at a human equivalent concentration. The default calculation of an HEC for a particle exposure uses the ratio of animal-to-human regional deposited dose (RDDR) to a specific region of the respiratory tract. The methods also allow replacement of the default approach when a better model is available. The derivation of the RfC in this case makes use of the Yu and Yoon (1990) model to calculate the HEC from the rat studies. Since the Yu and Yoon model has been developed only for the rat-to-human extrapolation, the chosen approach assumes that dosimetric differences between rats and other small-animal species would not result in a substantially lower HEC. The LOAEL (HEC) and NOAEL (HEC) from the rat studies based on the Yu and Yoon model are 0.36 and 0.155 mg/m^3, respectively.

6.6.2. Application of the Benchmark Dose Approach to Derivation of the RfC

An alternative to deriving the RfC based on the NOAEL identified in the animal studies is application of the BMC approach. The BMC was described by Crump (1984) and recently discussed by EPA (1995b). The BMC approach involves fitting a dose-response function to dose and effect information from a single study and using the dose-response curve to predict the dose

that will result in a response that is defined a priori as the benchmark response. For example, a 10% increase in incidence of epithelial hyperplasia might be defined as the benchmark response, and a dose-response curve relating inhaled DPM to hyperplasia in rats chronically exposed to diesel exhaust would be used to estimate the exposure concentration resulting in a 10% increase. The lower confidence limit of that concentration is the BMC, and it is used as the representative value for the dose-response assessment.

Several key issues concerning the derivation and interpretation of BMCs, especially in a comparative manner over a variety of studies with a myriad of endpoints with differing types of data such as with diesel, are yet to be resolved by the Agency. Several principal limitations are the following:

- Some key studies in rats have inadequate quantitative data for BMC.
- The scientific criteria for selecting BMC from many endpoints remains to be established.
- A deposition model is available only for rats (it is not clear how to compare BMCs based on deposition/retention models with BMCs based on default duration-adjusted concentrations).

Because of the issues and questions raised by these aspects of the BMC approach, the BMC will not be used to derive the RfC at this time.

6.7. DERIVATION OF THE INHALATION RfC

6.7.1. The Effect Level—A NOAEL From a Chronic Inhalation Study

Based on the analysis above, the studies of chronic exposures to diesel emissions performed at ITRI and HERP (Ishinishi et al., 1988; Mauderly et al., 1988) were selected as the basis of the RfC, because they identify both a NOAEL and a LOAEL for rats exposed chronically, because they identified the highest NOAEL (Table 6-2), and because they are thoroughly reported. The only other study identifying both a NOAEL and a LOAEL was the GM study, which was not used because information characterizing the pulmonary lesions in rats was limited. The availability of the dosimetric model for rats and not for other species, along with the apparent comparability between the rat and other rodent species in response, are also contributory to choosing the rat as the basis for developing the RfC. Although the data from the monkey in the Lewis et al. (1989) study suggest that the pulmonary function effect in primates more closely resembles that in humans, this study had only one exposed group, making evaluation of dose response impossible. Thus, these data are not sufficiently robust for derivation of an RfC but may be used as supporting information. The pulmonary effects, including histopathological lesions, biochemical changes, pulmonary function impairment, and impaired particle clearance, were

determined to be the critical noncancer effect. Sufficient documentation from other studies showed that there is no effect in the extrathoracic (nasopharyngeal) region of the respiratory system or in other organs at the lowest levels that produces pulmonary effects in chronic exposures. The exposure concentration of 0.46 mg/m^3 from the study of Ishinishi et al. (1988) is the NOAEL. Application of the dosimetric model of Yu and Yoon (1990) to this value resulted in a NOAEL(HEC) of 0.155 mg/m^3.

6.7.2. Application of UFs—Animal-to-Human and Sensitive Subgroups

Principal areas of uncertainty for this assessment are the human-to-sensitive human and animal-to-human extrapolations (Table 6-1). Because the RfC is based on a NOAEL from a chronic animal study, neither LOAEL-to-NOAEL nor subchronic-to-chronic extrapolations are needed. Also, the database for diesel is robust, with numerous well-conducted chronic studies in addition to information showing no adverse effects on development in two species or on reproduction in a two-generational study, all of which serve to eliminate the need for a UF for database deficiencies.

No quantitative information exists regarding subgroups that may be sensitive to the effects of diesel exhaust or DPM. The information available on enhanced allergenic effects discussed above and in Chapter 7 suggests that individuals already sensitized by various antigens are more sensitive to exposure to DPM than are those who are not, especially when undergoing an allergenic inflammatory episode. However, no quantitation of the relative sensitivity is available. Nor is there information indicating that children or male or female neonates are especially more or less sensitive. Therefore the default value of 10 is used to accommodate human-to-sensitive human extrapolation (Table 6-1).

Several issues reside in applying the UF for animal-to-human extrapolation to the diesel database. First, the PK component of this UF (see Table 6-1) has been addressed by the application of a dosimetric model to obtain a HEC, thereby decreasing the UF to 3 (or $10^{0.5}$) for the residual PD component. Second, information discussed above and in Chapter 6 indicates that for certain endpoints such as chronic inflammation, the rat appears to have a more sensitive response than other species, including humans. That rats are more sensitive to the effects of inhaled DPM than are humans could be considered evidence sufficient to eliminate the remaining PD component of this UF. However, mode-of-action evidence for the various effects observed with diesel, especially pulmonary histopathology and immunologic effects such as enhanced allergenicity, indicate that events stimulatory to inflammatory processes underlie these effects, i.e., neutrophilic inflammation preceding fibrogenesis and such events as increased cytokine production preceding immunologic effects. Although indications are that humans are less sensitive than are rats to the inflammatory-mediated endpoint of fibrogenesis, it is problematic to

presume that humans would also be less sensitive to other inflammatory-mediated endpoints such as enhanced allergenicity that are now documented in the literature. In consideration of this missing specific mode-of-action information on inflammation, the PD component is retained at the value of 3.

The total composite UF is therefore 10 × 3 = 30.

The resultant RfC = $\frac{\text{NOAEL(HEC)}}{\text{UF}} = \frac{0.155\ \text{mg/m}^3}{30} = 5\text{E-}3\ \text{mg/m}^3\ (5\ \mu\text{g/m}^3)$

6.7.3. Designation of Confidence Level

The studies used as the basis for the RfC were well-conducted chronic studies with adequate numbers of animals, in which the target tissues (i.e., the respiratory tract) were thoroughly examined and in which the LOAELs and NOAELs were consistent across studies. The database contains several chronic studies, including multiple species, that support the LOAEL observed in the principal study. The availability of multiple chronic studies all having consistent effect levels imparts a high confidence to the principal study. Developmental and multigeneration reproductive studies also exist, resulting in a high-confidence database. The endpoints chosen have relevancy to the human response to other poorly soluble particulates.

The modeling employed in this assessment to derive HECs includes both deposition and clearance mechanisms, although assumptions have been made with certain of the clearance parameters. Current mode-of-action information indicates that events stimulatory to inflammatory processes underlie the effects reported in the pulmonary (target) tissues. Continued investigation in this area may clarify the status of other effects (e.g., immunologic) reported from diesel exposure.

The application of this RfC to general ambient particulate matter such as $PM_{2.5}$ must be limited. Compared with $PM_{2.5}$, DPM has a relatively high organic content and a preponderance of small particles capable of penetrating to the lung. As a consequence, DPM may be considered a subcategory of $PM_{2.5}$, with perhaps a greater potential for eliciting toxicity.

High confidence in both the studies and database leads to high confidence in the RfC itself.

6.8. SUMMARY

Table 6-3 summarizes the principal decision points in derivation of the diesel RfC, the Agency's estimate of a continuous inhalation exposure that is considered to be without an appreciable risk of deleterious noncancer effects during a lifetime.

Table 6-3. Decision summary for the derivation of the RfC for diesel engine emissions

Critical effect	Pulmonary histopathology in rats
Principal study	Ishinishi et al., 1988; Mauderly et al., 1988
NOAEL	0.46 mg/m^3
Model adjusted NOAEL = NOAEL(HEC)	0.155 mg/m^3
UFs	10—Human-to-sensitive human 3—Animal-to-human (pharmacodynamics)
Composite UF	30
NOAEL(HEC) / UF = RfC	0.155 mg/m^3 / 30 = 5E-3 mg/m^3
Confidence in the RfC	High

The derivation of this RfC was made in consideration of several candidate critical effects (including immunologic endpoints), in consideration of the relevancy of the critical effect chosen to the human response, and in recognition of the strengths and limitations of the modeling applied to obtain a human equivalent concentration (HEC).

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